

Application of a stochastic modeling to evaluate tuberculosis onset in patients treated with tumor necrosis factor inhibitors

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July 16, 2012

Abstract

This manuscript deals with the application of a stochastic model to face the risk of reactivation of latent tuberculosis infection in patients undergoing treatment with tumor necrosis factor inhibitors. Firstly, the paper reviews the approach proposed by R. S. Wallis, which consists in predicting the extent of side effects of a given drug through extremizing procedures on a simple set of parameters (such as the monthly rate of reactivation of a latent infection). Secondly, the paper develops an analytical analysis of this approach by stochastic modeling. The rate for emergence of reactivation of latent tuberculosis infection is investigated by means of Markov chains and an exact solution for its temporal evolution is obtained. The analytical solution is compared with Monte Carlo simulations and with experimental data, showing overall excellent agreement. The framework outlined in this paper is quite general and could be extremely promising in contributing further to detecting drug therapies side effects and could develop a (hopefully fruitful) bridge between the physician and the physicist viewpoints.

1 Introduction

Over the last decades, the improved understanding of the pathogenesis of chronic inflammatory diseases together with a major advance in biotechnology have accelerated the development of highly selective biological therapies, designed to neutralize specific targets that mediate and sustain the clinical manifestations of diseases [1, 2, 3]. These compounds, mainly monoclonal antibodies (mAb) and fusion proteins, introduced a breakthrough in the management of different conditions including inflammatory rheumatologic disorders [3]. In this context, the first setting of application of the biological agents was rheumatoid arthritis (RA), a chronic autoimmune disease affecting approximately 1% of the adult population [4]. If the disease is not treated adequately, progressive deformity can lead to loss of quality of life and reduce average life expectancy by about a decade [4]. Studies on the pathogenic mechanisms of RA have revealed that tumor necrosis factor (TNF) is a cytokine playing a critical role in the inflammatory cascade that results in the irreversible joint damage typical of the disease [5]. Following these discoveries, a series of clinical trials in patients with RA showed the therapeutic benefit of TNF blockade [6]. As a consequence, five biological agents engineered to block TNF actions are currently available: infliximab, adalimumab, golimumab, certolizumab pegol (all of them mAb), and etanercept (a receptor fusion protein) [7]. While being highly effective, TNF blockers have raised concerns about the potential for an increased susceptibility to infections, in particular the reactivation of latent tuberculosis (TB) infection [8]. This is caused by *Mycobacterium tuberculosis*, which may be delighted by an extremely metastable latency lasting for decades. TNF is involved in both protection against mycobacterial infection and TB pathogenesis, since it is required for the formation of granulomas, which sequester *Mycobacteria* and prevent their dissemination [8]. The reactivation of latent TB infection has been associated with all TNF inhibitors, hence pre-initiation screening procedures have been recommended, which have successfully reduced the number of reported cases [9].

R. S. Wallis and coworkers, in a series of papers [10, 11, 12, 13] belonging to the medical literature, reported the most extensive and detailed studies about the relationship between the use of TNF antagonists and the onset of several granulomatous infections, with particular emphasis on TB.

From data collected through the Adverse Event Reporting System of the USA Food and Drug Administration in the time-window 1998–2002, considering two test-case drugs with a different mechanism of action (i.e. infliximab and etanercept), one can check that granulomatous infections involve 54 over 10^5 patients treated with

infiximab and 28 over 10^5 patients receiving etanercept [13]. Therefore, the question is: As the latency in TB can last decades, are these infections (in patients under therapy) new ones or are they reactivation of previously encountered pathogens due to a suppressed immune system? The answer is by far not trivial as, for TB, there are no secure pathways to discriminate between a new infection or the raise of a previous one. Moreover, a clear methodology for finding latencies is still lacking.

Furthermore, the rarity and different characteristic sizes of this infection in different countries (ranging from e.g. 5 over 10^5 in Sweden up to e.g. 140 over 10^5 in Romania [11]) implies that data analysis and its subsequent interpretation must be carefully performed.

In order to tackle the above-mentioned problem, one could rely on the molecular details of TNF processing signal, which has been (at least partially) elucidated (see e.g. [14]), and on a clear rationale in understanding features and limitations of infiximab and etanercept therapies, which could be achievable directly through molecular immunology approach. Beyond these "standard" strands, a completely different route can also be performed.

Given the relative huge amount of collected data, the problem can also be considered from a purely inferential viewpoint, by-passing the underlying molecular immunology know-how. According with this perspective, in Ref. [12], an abstract (logical) environment has been defined, where patients can occupy one of the five different states: (0) No infection, (1) New infection, (2) Latency, (3) Reactivation of a previous TB infection, (4) Post primary TB. Now, the patients starting the therapy (and hence belonging to the survey whose data have been collected) can correspond to either state (0) or (2), because, clearly, all the other states imply quantifiable sickness and the patient would then be treated for TB rather than RA. Then, at the end of the survey, a fraction of these patients will be in an illness state, i.e. either state (3) or (4). The transition rates between different states are assumed as free-parameters and, e.g. via Monte Carlo simulations, one can find the most probable rates as those able to reproduce, with the smallest error, the experimental data. Interestingly, by comparing the parameters obtained by this extremizing procedure, one can conclude that the main difference between infiximab and etanercept therapies resides in the largely different rates of reactivation of a preexisting infection, which in case of patients treated with infiximab is one order of magnitude higher.

Moreover, the approach is remarkable not only as far as RA drug usage is concerned, but also from a modeling point of view as it does not employ any biological or medical detail, that is, it is based solely on statistical inference and extremization

procedures on a (reasonable) ensemble of data¹. Consequently, the method could be, in principle, of widespread generality and this last point motivates further our investigation.

Starting from the framework introduced by R. S. Wallis, we formalize the time evolution of the system as a stochastic process and we describe it in terms of a Markov chain. The latter is solved both analytically and numerically (through Runge-Kutta algorithm) and further confirmed through our Monte Carlo tests. In particular, the analytical solution allows to obtain a simple functional form for the number of patients affected by TB versus time and to evidence qualitative differences between different drugs; it also allows to detect a set of integrals of motion underlying hidden symmetries.

2 The model

In this section we formalize the model introduced in [12]. Such probabilistic model is based on purely clinical variables with the aim of reproducing data of TB onset in patients treated with TNF inhibitors, with particular attention on infliximab (an anti-TNF mAb) and etanercept (a soluble TNF receptor).

The model, whose structure is depicted in Figure 1, consists in identifying a set of possible states² for the patient subjected to drug treatments, and in fixing the likelihood for the patient to change his/her state. In mathematical terms, we need to fix the transition rates per unit time, where the timescale is set by the frequency of data collection, which here is one month.

The clinical states available to a test-patient are taken as (see Figure 1) follows:

- 0 : Absence of infection;
- 1 : New infection (that after one month can give rise either to active TB or latent infection);
- 2 : Latent infection;
- 3 : Reactivated TB after latency;

¹The last point is of fundamental importance because, in order to link the predicted probability obtained by the mathematical procedure with the observed frequency of the reported cases, one invokes the first postulate of probability theory, which states that for an infinite number of cases probability and frequency do coincide and the larger the sampling, the smaller the difference between them.

²Clearly, on large samples, sudden incidents may appear to some patients (e.g. death for other causes) or some others may assume both the drugs: the analysis has been previously purified from these cases [12, 13].

4 : Active TB with onset one month after the infection.

Moreover each patient is assumed to monthly change his/her state, following the corresponding transition probabilities, which constitute the model parameter set. Using t to label the time, these probabilities are:

L : Probability of having a latent infection at the beginning of the observation ($t = 0$), while, obviously, $(1 - L)$ is the probability of not having any infection at that moment;

N : Monthly rate of TB infection during the observational time;

P : Probability of a new TB infection to become active TB after one month; as a consequence, $(1 - P)$ is the probability of this new infection to give rise to a latent infection;

R : Monthly rate of reactivation of a latent TB infection;

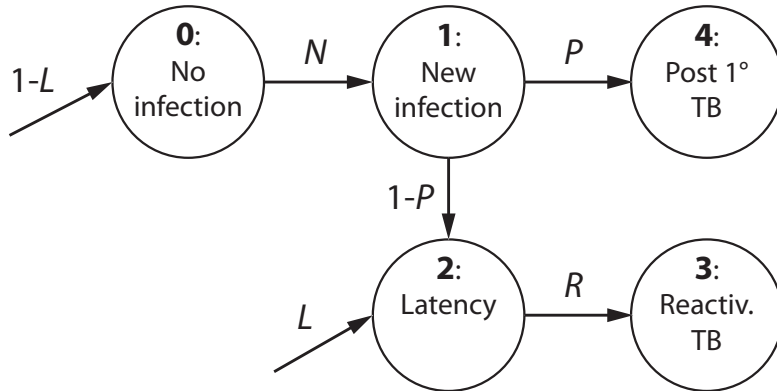


Figure 1: Symbolic representation of the Markov chain under investigation.

It is worth noting that the available data consist in a collection of times corresponding to the onset of TB (in its active phase, namely a detectable scenario) after the beginning of the treatment with TNF blockers. As a consequence, the only states which are possible to observe are the states 3 and 4.

Unfortunately, as widely discussed in the introduction, these states (that account for ill patients) are not distinguishable one respect to the other simply by looking at the data (hence motivating both Wallis study and our mathematical deepening), however, some progress can be made using stochastic extremization (whose most famous example is Monte Carlo simulation). The idea resembles the standard maximum likelihood and it consists in finding the best values for free parameters such that the theoretical curves collapse over the experimental data [15, 16].

As already outlined, following this procedure, the main result in [12] is that the principal difference between infliximab and etanercept treatments resides in different management of latent TB. The former seems to enhance reactivation of one order of magnitude more than the latter.

2.1 Markov chains and master equations

The model described in the previous section can be converted into differential equations coding for the temporal evolution of the probability of patient's states (which, we stress once more, can be compared to the corresponding fractions over a sample of patients given the huge collection of data).

Being the states discrete, this can be accomplished in complete generality using Markov chains (see Figure 2), namely a (discrete-time) probabilistic framework where the probability of being in a given state (say B , Figure 2) at a given time t depends only on the probability distribution over all the states (connected to B , hence both A and C again in the toy-example reported in Figure 2) at the last time step $t - 1$ and on the transition rates linking these states (to B , hence $w_{B \leftarrow A}$ and $w_{C \leftarrow B}$).

In fact, as we can see, it is instructive to start considering the toy Markov Chain with only three states (A , B and C), non-null transition rates $w_{B \leftarrow A}$ and $w_{C \leftarrow B}$ and time step Δt , shown in Figure 2.

Note that, in the model, the probabilities of going from A to B and from C to B exist but not the opposite ($w_{B \rightarrow A} = 0$, $w_{C \rightarrow B} = 0$) hence, if the initial state is all concentrated in C , there will be no evolution, while if the starting point is spread among A and B , after enough time, the probability distribution will be peaked on C only (but in its -finite- temporal evolution resides our interest).

It is then intuitive to understand that the probability p of being into the state B at time $t + \Delta t$ is given by the probability of already being in B (hence $p_B(t)$) plus the probability of arriving in B from A times the probability of being in A at the previous step (hence $w_{B \leftarrow A} P_A(t)$) minus the probability of leaving B to C times the probability of being in B at the previous step (hence $-w_{B \leftarrow C} P_B(t)$); this concept can be written as follows:

$$p_B(t + \Delta t) = p_B(t) + p_A(t) w_{B \leftarrow A} \Delta t - p_B(t) w_{C \leftarrow B} \Delta t . \quad (1)$$

Since the mathematics for continuous variable differential equations is much more handily and does not change significantly the perspective if the time step is small with respect to the global time window (in our case, the time step is one month and

the time window four years), we are allowed to consider the time as a continuous variable. This can be achieved straightforwardly starting by the previous equation using a limit procedure:

$$\lim_{\Delta t \rightarrow 0} \frac{p_B(t + \Delta t) - p_B(t)}{\Delta t} = \frac{dp_B(t)}{dt} = p_A(t)w_{B \leftarrow A} - p_B(t)w_{C \leftarrow B}.$$

The evolution for the probability $p_B(t)$ is then ruled by the following differential equation, namely a "Master Equation", which acts as a continuous counterpart of the Markov-chain in the discrete-time case:

$$\frac{dp_B(t)}{dt} = p_A(t)w_{B \leftarrow A} - p_B(t)w_{C \leftarrow B}. \quad (2)$$

In general, for a system that can be in one of N states, we need a $N \times N$ transition matrix w (where $w_{j \leftarrow i}$ is the rate for the transition from state i to state j) and the master equation takes the form

$$\frac{dp_i}{dt} = \sum_{j=1}^N w_{i \leftarrow j} p_j(t) - \sum_{j=1}^N w_{j \leftarrow i} p_i(t). \quad (3)$$

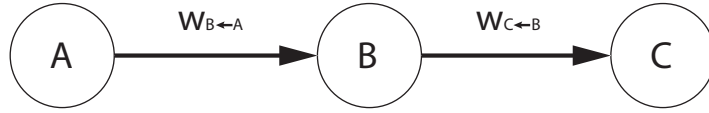


Figure 2: Toy Markov chain: From the state A there is a potential flux of probability at rate $w_{B \leftarrow A}$ toward the state B , hence we expect that, after a proper amount of time, some of the probability p will be drained from A to B . The same holds for the situation linking C to B . After an infinite time the probability of having the patient into the state C would be one, while being zero for the states A, B .

3 Master equations for Wallis model

Keeping in mind Figure 1 and the previous toy model, we can write down the system of differential equations describing the evolution of the five states earlier

introduced as follows:

$$\begin{cases} \frac{dp_0}{dt} = -N p_0(t), \\ \frac{dp_1}{dt} = N p_0(t) - p_1(t), \\ \frac{dp_2}{dt} = (1 - P) p_1(t) - R p_2(t), \\ \frac{dp_3}{dt} = R p_2(t), \\ \frac{dp_4}{dt} = P p_1(t), \end{cases} \quad (4)$$

with initial conditions

$$\begin{cases} p_0(t = 0) = 1 - L, \\ p_2(t = 0) = L, \\ p_1(t = 0) = p_3(t = 0) = p_4(t = 0) = 0. \end{cases} \quad (5)$$

The numbers indexing the probabilities mirror the enumeration of the previous section, hence p_0 stands for the probability for a patient to be into the state 0 and so on.

Note that, as patients affected by active TB do not start RA therapy, we set $p_1(t = 0) = p_3(t = 0) = p_4(t = 0) = 0$. Furthermore, the parameter L tunes the initial amount of latent-TB patients with respect to free-TB patients, such that for $L = 0$ all patients are healthy, while for $L = 1$ all patients display a latent TB-infection;

The solution of these equations can be easily obtained using first order ordinary differential equations theory and the results assume the following forms:

$$\begin{cases} p_0(t) = (1 - L) e^{-Nt}, \\ p_1(t) = N \frac{1-L}{1-N} (e^{-Nt} - e^{-t}), \\ p_2(t) = \left[L + \frac{(1-P)(1-L)N}{(N-R)(1-R)} \right] e^{-Rt} + \frac{(1-P)(1-L)N}{(1-N)(1-R)} e^{-t} - \frac{(1-P)(1-L)N}{(1-N)(N-R)} e^{-Nt}, \\ p_3(t) = -\frac{R(1-P)(1-L)}{(1-N)(N-R)} (1 - e^{-Nt}) + \left[L + \frac{(1-P)(1-L)N}{(1-R)(N-R)} \right] (1 - e^{-Rt}) \\ \quad + \frac{(1-P)(1-L)RN}{(1-N)(1-R)} (1 - e^{-t}), \\ p_4(t) = P \frac{1-L}{1-N} (N e^{-t} - e^{-Nt} + 1 - N). \end{cases} \quad (6)$$

Of course, since the total amount of patients is conserved, $C_0 = p_0 + p_1 + p_2 + p_3 + p_4$ is an integral of motion, that is

$$0 = \frac{d}{dt} C_0 \Rightarrow C_0 = p_0(t) + p_1(t) + p_2(t) + p_3(t) + p_4(t) = \text{const.} \quad (7)$$

Beyond C_0 , the system above admits another integral of motion C_1 , namely

$$0 = \frac{d}{dt} \left[p_2(t) + p_3(t) + \frac{P-1}{P} p_4(t) \right] \Rightarrow C_1 = p_2(t) + p_3(t) + \frac{P-1}{P} p_4(t) = \text{const.} \quad (8)$$

This means that the rate of growth for patients in the latency branch (i.e. in states 2, 3) equals the rate of growth for remaining infected patients (i.e. in state 4) weighted by a factor $P^{-1} - 1$, so that the smaller P and the larger the difference between the related rates. The knowledge of integrals of motion can be very useful as they allow to obtain information in a very simple way; for instance, if at any time P decreases, $p_4(t)$ must also decrease (or, analogously, $p_2(t) + p_3(t)$ must increase) in order to maintain C_1 constant. Given C_0 and C_1 , other integrals of motion which are combination of C_0 and C_1 , can be trivially built. For example, $C_2 = C_0 - C_1$ fulfills

$$0 = \frac{d}{dt} \left[p_1(t) + p_0(t) + \frac{1}{P} p_4(t) \right] \Rightarrow C_2 = p_1(t) + p_0(t) + \frac{1}{P} p_4(t) = \text{const.} \quad (9)$$

We underline that this kind of investigation can be accomplished only through an analytical study of the system.

As discussed above, the fraction of active TB cases is given by the sum of the fraction of cases of direct TB after infection and of the fraction of cases with reactivated TB; namely, calling $c(t)$ the total fraction of cases, we have:

$$c(t) = p_3(t) + p_4(t). \quad (10)$$

In the above quantity, the time dependence appears only through three different exponential decay terms (e^{-t} , e^{-Nt} , e^{-Rt}), which vanish at infinite time, so that the solution becomes a constant term equal to 1, meaning that, if we wait for a sufficient long (possibly infinite) time, all patients become sick (despite obviously they can eventually die much earlier by all the reasons not accounted in their link with RA/TB). To deepen the temporal evolution of these probabilities at not so long times, it is useful to use a little bit of algebraic manipulation to isolate these constant and decay terms and rewrite the evolution in time of $c(t)$, namely the fraction of activated TB cases, as follows:

$$c(t) = 1 + k_1 e^{-t} + k_R e^{-Rt} + k_N e^{-Nt}, \quad (11)$$

where the three new constants k_1 , k_R and k_N are related to the clinical parameters

by

$$\begin{cases} k_1 = N \frac{(1-L)}{(1-N)} \left(P - R \frac{(1-P)}{(1-R)} \right), \\ k_R = -L + \frac{N(1-P)(1-L)}{(1-R)(R-N)}, \\ k_N = -\frac{(1-L)}{(1-N)} \left(P + R \frac{(1-P)}{(R-N)} \right). \end{cases} \quad (12)$$

It is worth noticing that in the limit of long time, the exponential terms are vanishing in such a way that $c(t)$ converges to 1, as expected:

$$\begin{aligned} \lim_{t \rightarrow \infty} c(t) &= 1, \\ \lim_{t \rightarrow \infty} p_3(t) &= 1 - P(1 - L), \\ \lim_{t \rightarrow \infty} p_4(t) &= P(1 - L). \end{aligned} \quad (13)$$

Before turning attention to the approximations that better highlight the scenario of smaller time windows, we stress the perfect agreement between our analytical solution (6), its numerical approximation via fourth-order Runge-Kutta algorithm, the Monte Carlo simulations³ and real data as shown in Figure 3.

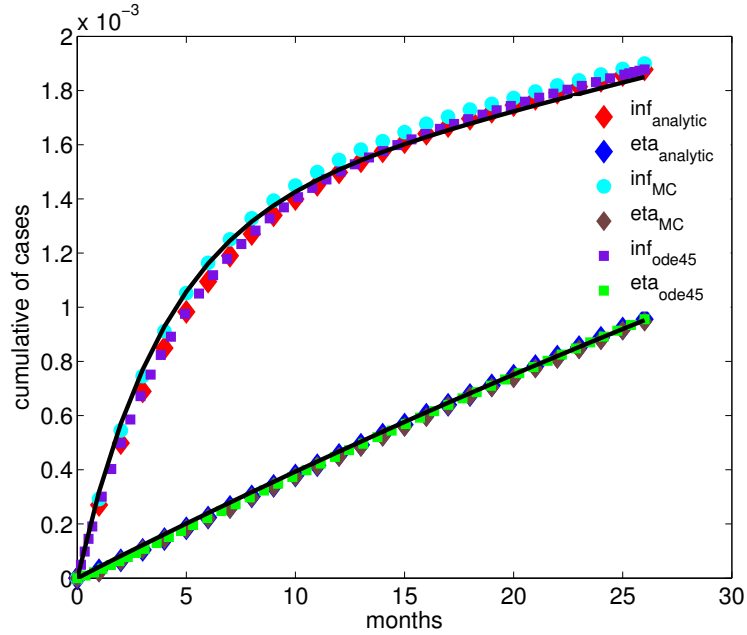


Figure 3: Comparison between analytical, numerical (Ruge-Kutta algorithm, *ode45* in Matlab), Monte Carlo (over a population of 10^7 virtual patients) solutions and real data. Note that real data are the continuous (black) curves, which are not represented in the legend for the sake of visibility.

³For a Monte Carlo simulation we mean a simulation in which a set of virtual patients evolves in time following the Markov chain of Figure 1 giving a sample of the evolution of the fraction of cases during time.

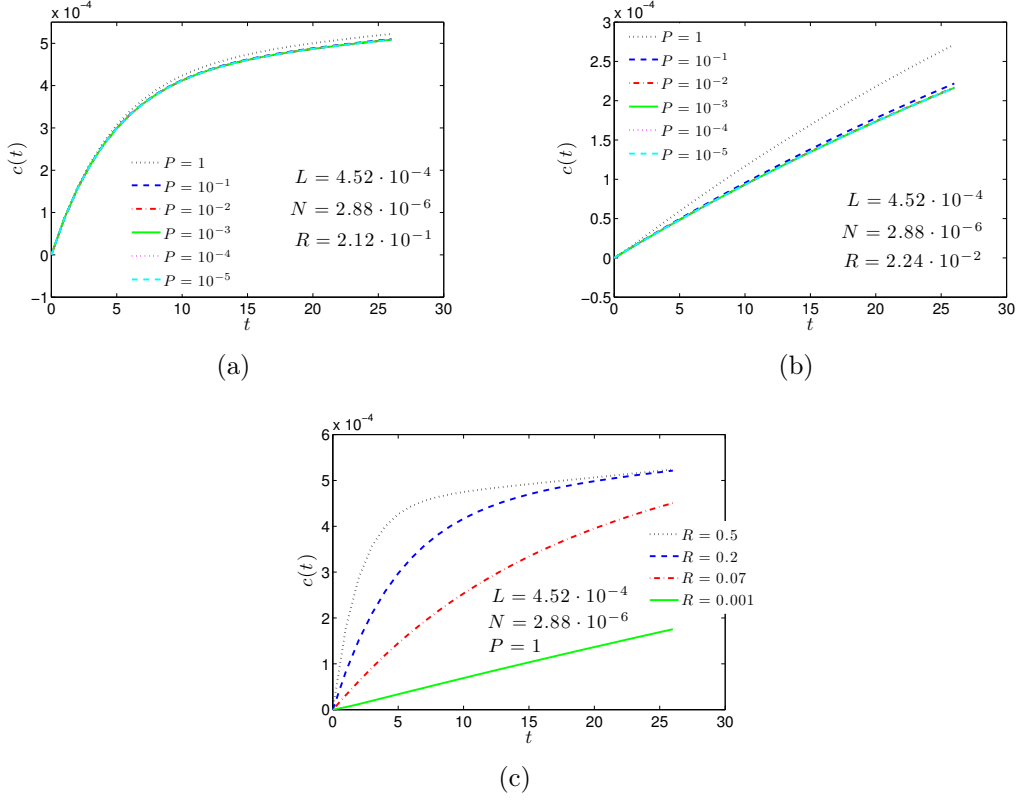


Figure 4: Time evolution of the complete solution $c(t)$ with the parameters fixed according to our best fits (see Table 1). Through the overlapping of the curves in panels (a) and (b) it is possible to note the mild role played by P .

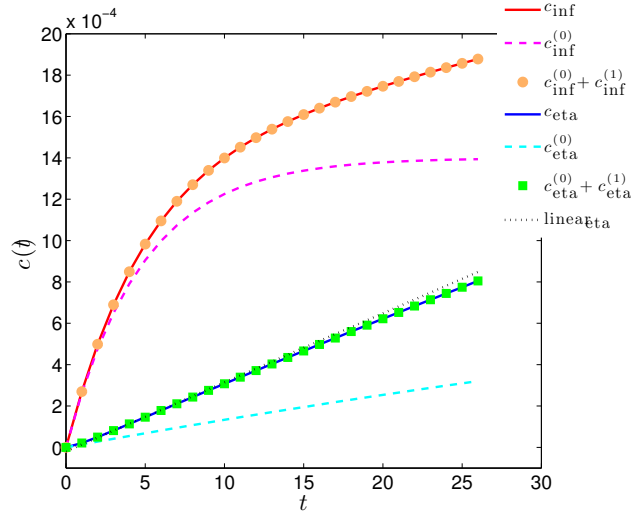


Figure 5: Comparison among the exact solution $c(t)$ of Eq. (11), the approximate solution $c^{(0)}(t)$ (where $\mathcal{O}(N)$ terms are neglected) and the approximate solution of Eq. (14) where a higher order $c^{(1)}(t)$ is retained. For etanercept parameters also the linear approximation (15) is shown.

3.1 Useful approximations: What we learn by studying the model

While we get the complete solution of the model, from a practical perspective, it would be useful to find proper approximations which would not significantly affect the behavior of $c(t)$, but offer a much more handy interpretation of the results.

In particular, Eq. (11) can be reduced to a simpler form if we note that the monthly rate of TB infection N is much smaller than all the other parameters, in agreement with studies on TB and with results found in [12] and, a posteriori, in the current paper (see Table 1).

Hence, as a first approximation step, we assume $N \ll 1$ and $N/R \ll 1$ such that we can expand the solution at the first order in N and N/R , as follows:

$$\begin{aligned} k_1 &= (1-L) \left(P - R \frac{1-P}{1-R} \right) N [1 + N + \mathcal{O}(N^2)], \\ k_R &= -L + \frac{(1-P)(1-L)}{R(1-R)} N \left[1 + \frac{N}{R} + \mathcal{O}\left(\frac{N^2}{R^2}\right) \right], \\ k_N &= -(1-L) \left\{ P[1 + N + \mathcal{O}(N^2)] + (1-P)[1 + N + \mathcal{O}(N^2)] \left[1 + \frac{N}{R} + \mathcal{O}\left(\frac{N^2}{R^2}\right) \right] \right\}. \end{aligned}$$

Therefore, we can write the following approximation

$$\begin{aligned} c(t) &= 1 + (1-L) \left[P - R \frac{1-P}{1-R} \right] N e^{-t} + \left[-L + \frac{(1-P)(1-L)}{1-R} \frac{N}{R} \right] e^{-Rt} \\ &\quad - (1-L) \left[2P(1+N) + \frac{N}{R}(1-P) \right] e^{-Nt}, \end{aligned} \tag{14}$$

where we neglected terms of order $\mathcal{O}(N^2)$, $\mathcal{O}(N^2/R)$ and $\mathcal{O}(N^2/R^2)$. By using the parameter values found by Wallis to fit the data of patients treated with infliximab and etanercept, this approximation is extremely accurate as we can check in Figure 5.

Let us now move further and focus on the exponential terms. First, we notice that $e^{-t} \ll e^{-Rt} \ll e^{-Nt}$, due to the fact that $1 \gg R \gg N$. Moreover we can neglect the term e^{-t} , as it decays very quickly and the factor k_1 is of order $\mathcal{O}(N)$, and we can expand e^{-Nt} as $e^{-Nt} \approx 1 - Nt$, given that $Nt \ll 1$, namely $N \ll 10^{-2}$. As for e^{-Rt} , a similar approximation ($e^{-Rt} \approx 1 - Rt$) can be adopted as long as $R \lesssim 10^{-2}$. Thus, for times $1 \ll t \ll 1/R \ll 1/N$, we can write the following *linear* approximation

$$c(t) \approx 1 + k_R(1 - Rt) + k_N(1 - Nt). \tag{15}$$

The above approximation is rather good for etanercept-treated patients, as shown

in Figure 5. On the other hand, if we consider infliximab-treated patients, this approximation does not fit data. In fact, the expansion for e^{-Rt} does not hold because now $R \approx 10^{-1} \text{month}^{-1}$ and Rt is no longer small.

Moreover it may be stressed that, in the regime $N \ll (1, P, R, L)$, considering R and P as the parameters that can be affected by the treatment (as justified above), the most relevant parameter in ruling the solution behavior is R . In fact by plotting the solution and varying the order of magnitude of P (Figure 4(b) and 4(c)) and R (Figure 4(a)) it is possible to note the small effect of a coarse tune of P with respect to that of R . A qualitative argument in favor of this claim is that in the zero approximation of the solution (i.e. neglecting even terms $\mathcal{O}(N)$) P does not appear at all.

	Best Fits
L	$4.52 \cdot 10^{-4}$
N	$2.88 \cdot 10^{-6}$
R_{INF}	$2.12 \cdot 10^{-1}$
P_{INF}	$9.76 \cdot 10^{-1}$
R_{ETA}	$2.24 \cdot 10^{-2}$
P_{ETA}	$8.03 \cdot 10^{-1}$

Table 1: Best fit parameters obtained through least square method. All values are expressed in units months^{-1} .

To summarize, our results confirm that the most important difference between drug therapies based on infliximab or etanercept is that the former enhances TB reactivation more than the latter: In agreement with Wallis results [12], we found $R_{INF} \sim 10 R_{ETA}$. However, as N is very small (of order $10^{-6} \text{months}^{-1}$) with respect to the experimental time-window (26 months), we can reasonably infer only the reactivation rate R , while the measure of P , is affected by a much larger uncertainty, so that the statement $P_{INF} \simeq P_{ETA}$ has to be claimed with more caution.

4 Summary and outlooks

In these notes we formalized, from a mathematical perspective, a recent series of papers by Wallis and coworkers [10, 11, 12, 13], where they developed a stochastic approach to data analysis in drug testing. In particular, we report the application of a stochastic model to face the risk of reactivation of latent TB infection in patients undergoing treatment with TNF inhibitors.

The approach introduced in [12] bypasses the underlying biological and medical

suggestions toward a completely different route, close to the general framework of stochastic data analysis. More precisely, the possible states of each patient are split in five different classes (healthy with no infection, new infection, healthy with a latent infection, reactivation of a latent infection, active TB), which reasonably cover the whole plethora of events. Then, arbitrary transition rates between these states are introduced, implicitly defining a Master Equation and, through Monte Carlo simulations, the value of these rates are estimated as those that best approximate the experimental data.

In the present paper we gave a mathematical backbone to this approach, building it on explicit Markov processes, whose continuous limit gave us Master Equations governing the evolution of the probability of belonging to each of the possible states, that we solved in all details. We developed a clear mathematical machinery able to recover Wallis findings, in excellent agreement with both experimental data and the immunological perspective.

It is worth stressing that this methodology, being based on very standard procedures, has the advantage to hold beyond the test case of RA/TB. For instance, handling the complete (mathematical) solution allows to better account for reasonable approximations, tackling their control quantitatively (e.g. finding the proper timescales involved in the process or the integrals of motion constraining the evolution of the system). We hope that this test-case may shed light to future developments of this sideline approach in figuring out adverse events in drug therapies.

Acknowledgements

This work is supported by the FIRB grant RBFR08EKEV and by Sapienza Università di Roma.

The authors are extremely grateful to Prof. Robert S. Wallis for providing us data and for several fruitful suggestions.

AB is also grateful to Giancarlo Ruocco for acting as a tie between the two communities (physicists and physicians).

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